PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Vulnerability assessment tools for infectious threats and antimicrobial resistance: a scoping review protocol
AUTHORS	Jeleff, Maren; Lehner, Lisa; Giles-Vernick, Tamara; Dückers, M; Napier, A. David; Jirovsky, Elena; Kutalek, Ruth

VERSION 1 – REVIEW

REVIEWER	Kyle B. Enfield, MD FSHEA FCCM University of Virginia United States
REVIEW RETURNED	21-Jun-2019

GENERAL COMMENTS	Well developed and needed review with a well thought out search strategy.

REVIEWER	Payal K. Patel VA Ann Arbor Healthcare System and University of Michigan, Ann Arbor, MI, USA
REVIEW RETURNED	24-Jun-2019

GENERAL COMMENTS	This is a very interesting project by Jeleff et al. that aims to do a scoping review protocol looking at vulnerability assessment tools for antimicrobial resistance and infectious disease outbreaks. I have a few comments that may strengthen the work. Methods: Why did the authors not use pubmed? If there is rationale as to why, may mention in the manuscript or consider adding. I think its definitely a strength that you are looking at the book chapters and grey literature, especially for this topic. I would add into the methods who the initial two reviewers are (by initials if authors and would describe their scientific background) and would do this for the four researchers doing the data abstraction as well. This helps the reader understand more about the process. In the methods, I would recommend pre-selecting about 5 key papers that should reflect what you think should come up in the results, perhaps landmark papers and reference them in this protocol. The search strategy should then be tested to ensure these papers are actually captured in the search. This will strengthen your methods. Who will be at the discussion rounds mentioned in the methods—please specify. Make sure you spell out SoNAR-Global partners in the manuscript and abstract If in the final product of this, you can make this open access and have hyperlinks to the tools you do find—this could be high yield for

	the groups you're targeting most—I would try to make sure that's the way it looks in the final publication once the review is done.

REVIEWER	Ben Oppenheim Metabiota
REVIEW RETURNED	15-Jul-2019

GENERAL COMMENTS	Overall: This proposed study has a fascinating and important objective, and I really commend the authors for submitting the protocol for review and publication. The design has several key areas where I think significant additional clarification and structure is needed. I hope the comments below are of use to the authors in the design and development of this study, and in revising the article. —— The general purposes and aims of this study are fairly clear, but the introduction could be sharpened in order to better specify the research question. Within the introduction itself, the authors state that "Our purpose, therefore, is to understand the barriers that keep community members in crisis contexts from representing their own needs." In the next paragraph, the goal of the study shifts, and is summarized as follows: ". To determine the most effective vulnerability assessment tools available, we will map existing tools for assessing locally relevant case definitions of vulnerability." The authors may be saying that the most effective assessments tools allow particular communities to identify their own needs, from which relative and absolute levels of vulnerability can be inferred, but it's not clear. Then on p. 6 the study objective appears again but is posed somewhat differently: "- Systematically review and appraise existing instruments to assess human vulnerability and factors associated with the incidence and spread of infectious diseases and AMR - i.e. through interactions of humans, animals and surrounding environments; - Discern overlaps and gaps among the tools" The focus is now not just identifying the best tool for assessing the vulnerability of particular groups in society, but to assess drivers of outbreak risk. What I would quite strongly suggest is that the authors take a step back, and begin by specifying what they mean by vulnerability. The rationale suggests vulnerability relates to group level inequalities that exposure particular populations or identity groups to more intense harm, conditional on an outbreak occurring. Text elsewhere suggests that vulnerability means something different, perhaps areas at elevated risk of outbreak in the first place. More substantively, the rationale for the study doesn't really make a clear case for including epidemic outbreaks and AMR in the same analytic framework and data collection exercise. These types of health threats can be driven by quite different societal, economic, epidemiological factors, to the extent that grouping may obscure more than it reveals. At minimum I'd suggest that the authors spend

	some time and text discussing why these types of health threats should be considered together, and ideally, what analytic leverage could be gained (and lost) by going this route. On p. 6, more explanation for why the PICO tool is being introduced would be helpful. What purpose does this particular framework serve? Is it to guide identification of tools (ie. a search method) or their assessment (a quality assessment framework)? p. 7: Population The list of pathogens with pandemic potential seems problematic. Most of these have zero pandemic potential: lassa, CCHF and RVF can cause localized epidemics, but not global spread. (relatedly: the authors could and should include a definition for infectious disease threat — this is the first time that pandemic risk is introduced as the key threshold of interest. Perhaps epidemic risk would make more sense)? The exclusion of coronaviruses (SARS, MERS), is also a strange omission. pp. 8-9: information sources the authors should be commended for seeking information from the grey literature, especially assessments by operational NGOs. It may also be fruitful to seek guidance from humanitarian communities of practice (SPHERE-related, ALNAP, WHO emergencies unit), to identify operational assessment tools. Other NGOs could include IRC, CARE. The World Bank may also have relevant tools, and certainly has vulnerability assessment methodologies. p. 10: inclusion criteria the focus on particular geographies (Uganda, Ukraine, Bangladesh) is introduced here for the first time. The meaning and implications of this choice are not quite clear, since the study also remains global (e.g. are the authors doing an exhaustive search but expending extra effort to capture tools from these countries? if so, why? are these context particularly interesting or representative of some broader set of country or contextual types? All of this should ideally be outlined in the protocol. p. 11 Here the protocol briefly discusses the outcome of the analysis: an analysis and comparison of the vulnerability assessment tools, and their strengths, weaknesses and gaps. It's unclear how the tools will actually be assessed: according to which criteria, and how these criteria will be measured. This is of course critical. Ideally the protocol would include the framework that the coders will use, as well as a rationale for the variables of interest. How should a vulnerability assessment tool be assessed? According to its design, how it requires that users gather and integrate data? It's not clear from the text in this draft, but an argument as to what matters would be important both to the success of the study, and to the literature more broadly.

REVIEWER	Mabel Carabali McGill University, Canada
REVIEW RETURNED	29-Jul-2019

GENERAL COMMENTS	The manuscript is a document considering an important public

	health topic. The document includes a protocol for a scoping review about vulnerability assessment tools for infectious diseases and antimicrobial resistance. Although the topic is very interesting, and it is an issue of international concern, the document as it is presented would benefit from major modifications before it is considered for publication, as follows: <u>Introduction:</u> The majority of statements require the support of references. Example, the sentence from line 23-27 in page 4, as the following two sentences in the same paragraph and the rationale statement. The entire section could be more concise, provide more definitions and present a clear research question. For example, “vulnerability” is not defined anywhere in the text, therefore the context for the review has not been clearly described. A brief mention of “vulnerable populations” was made in line 57 of page 4 but a definition of this or any other of the variables mentioned to be explored in the scoping review is not provided. <u>Methods:</u> There is no indication, in this section nor in the rationale, about the selection of the conditions to be studied. Furthermore, there is a broad scope in terms of EIDs but the mentioned ones are viral conditions, while one of the main topics are AMR, which are related mostly to conditions caused by bacteria. When presenting the “intervention section”, it was mentioned that the authors look for “disease outbreaks or epidemics complicated by AMR, to assess, evaluate, and identify vulnerable groups and practices.” It would be important for the eventual reader to understand what it means “complicated by AMR” or how, for instance, Ebola Virus is “complicated by AMR”. Several outcomes are mentioned in the document, but none is completely described or characterized. How would these outcomes would be ascertained? What specific information would the authors look for in the scoping review? Why would the authors look for data from 1978? Why the authors have a specific focus on Uganda, Ukraine and Bangladesh? Is this due to the availability or support from SoNAR partnership or would the review impact in other ways these countries? It would be important to describe the “simplified” version of the search strategy for Epistemonikos, Global index Medicus (WHO) and AJOL databases. It would be necessary to provide information and/or the rationale about why “certain” epidemiological studies and clinical will not be included and how this impact the review. It would necessary to provide the reference for the Rayyan QCRI application for data screening. Although it is understandable that a definitive data extraction chart does not exist at this stage; the manuscript would be improved, and its content would contribute more to the scientific

	community, if a template of the extraction sheet is provided. Based on the PRISMA-P checklist, several other items are missing in the proposed protocol. For example: • The rationale has not been comprehensively presented. • The list and definitions of the variables has not been comprehensively presented/addressed. • The list and definitions of the outcomes has not been comprehensively presented/addressed • Risk of bias was not assessed. This is important because despite the qualitative nature of the review, there should be a measure to address bias in the reviewed literature. • Information about how the data would be synthetized is not present. • Information about the assessment of the quality of the data was not presented.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (Kyle B. Enfield, MD FSHEA FCCM, University of Virginia)
RW1: Well developed and needed review with a well thought out search strategy.
Response: Thank you for your positive feedback.

Reviewer 2 (Payal K. Patel, VA Ann Arbor Healthcare System and University of Michigan)
RW2: This is a very interesting project by Jeleff et al. that aims to do a scoping review protocol looking at vulnerability assessment tools for antimicrobial resistance and infectious disease outbreaks. I have a few comments that may strengthen the work.
Methods: Why did the authors not use pubmed? If there is rationale as to why, may mention in the manuscript or consider adding. I think its definitely a strength that you are looking at the book chapters and grey literature, especially for this topic.
Response: Thank you for your valuable feedback. We selected the databases with the help of an experienced librarian of the University Library of the Medical University of Vienna. We chose Ovid's Medline over PubMed because a more nuanced search could be configured in Medline and because the databases provide similar content. Please find more information on this matter, following this link (provided by the University Library of the Medical University of Vienna):
https://wkhealth.force.com/ovidsupport/s/article/PubMed-vs-Ovid-s-Medline-1489081398582
Instead of searching two similar databases, we decided to use heterogeneous sources (e.g. Global Health database, Web of Science, AJOL and grey literature databases) to allow for differing contents. We added this information in the manuscript (line 251-257).

RW2: I would add into the methods who the initial two reviewers are (by initials if authors and would describe their scientific background) and would do this for the four researchers doing the data abstraction as well. This helps the reader understand more about the process.
Response: Thank you for your comment. We included author's initials to clarify who was involved in the screening, data extraction and full-text reading (line 64, 66 and line 305, 309, 317). We also included information on our scientific background (please see line 305 and 317).

RW2: In the methods, I would recommend pre-selecting about 5 key papers that should reflect what you think should come up in the results, perhaps landmark papers and reference them in this protocol. The search strategy should then be tested to ensure these papers are actually captured in the search. This will strengthen your methods.
Response: Thank you for your input. One of the authors (David Napier) developed a vulnerability

assessment tool and has used it in more than 30 countries. We used the “barefoot manual” (Napier 2013) as a reference paper. It is an easy to use manual to discern local-level vulnerabilities for effective resource allocation. We now included this information (line 246-249). As it is an unpublished paper it was not captured in the search. However, once we applied the search strategy we double checked the results.

RW2: Who will be at the discussion rounds mentioned in the methods—please specify.
Response: We added initials of the authors who conducted the discussion rounds (please see line 309).

RW2: Make sure to spell out SoNAR-Global partners in the manuscript and abstract
Response: Partners are mentioned in the abstract (page 3 “Ethics and Dissemination”, line 70-75) and we added a sentence on the network in the manuscript (line 116-118).

RW2: If in the final product of this, you can make this open access and have hyperlinks to the tools you do find—this could be high yield for the groups you’re targeting most—I would try to make sure that’s the way it looks in the final publication once the review is done.
Response: Many thanks for this valuable input. We will definitely do this.

Reviewer 3 (Ben Oppenheim, Metabiota)
RW3: This proposed study has a fascinating and important objective, and I really commend the authors for submitting the protocol for review and publication. The design has several key areas where I think significant additional clarification and structure is needed. I hope the comments below are of use to the authors in the design and development of this study, and in revising the article.
Response: Thank you very much for your thought-provoking and accurate input.

RW3: The general purposes and aims of this study are fairly clear, but the introduction could be sharpened in order to better specify the research question. Within the introduction itself, the authors state that “Our purpose, therefore, is to understand the barriers that keep community members in crisis contexts from representing their own needs.” In the next paragraph, the goal of the study shifts, and is summarized as follows: “To determine the most effective vulnerability assessment tools available, we will map existing tools for assessing locally relevant case definitions of vulnerability.” The authors may be saying that the most effective assessments tools allow particular communities to identify their own needs, from which relative and absolute levels of vulnerability can be inferred, but it’s not clear.
Then on p. 6 the study objective appears again but is posed somewhat differently:
“- Systematically review and appraise existing instruments to assess human vulnerability and factors associated with the incidence and spread of infectious diseases and AMR - i.e. through interactions of humans, animals and surrounding environments;
- Discern overlaps and gaps among the tools”

The focus is now not just identifying the best tool for assessing the vulnerability of particular groups in society, but to assess drivers of outbreak risk.
Response: We agree with your comment. As you mentioned, we are stressing that the most effective assessment tools allow particular communities to identify their own needs and assess locally relevant case definitions of vulnerability. However, our goal is also to find vulnerability assessment tools that are tailored to infectious threats (and AMR). A preliminary search yielded only few studies in this context. This is why we look for both a) local-level assessments and b) tools targeted at infectious threats. According to your comment, we revised the introduction and the objectives (please see line 89-141 and line 143-168).

RW3: What I would quite strongly suggest is that the authors take a step back, and begin by specifying what they mean by vulnerability. The rationale suggests vulnerability relates to group level inequalities that exposure particular populations or identity groups to more intense harm, conditional on an outbreak occurring. Text elsewhere suggests that vulnerability means something different, perhaps areas at elevated risk of outbreak in the first place.
Response: Thank you very much for your input. We substantially rewrote the introduction and contextualized the research according to your comment (please see line 89-141 and line 143-168). However, the scoping review explores and maps literature that addresses various definitions of vulnerability. Furthermore, we have experienced that some documents by NGOs (grey literature) often neither define "vulnerability" nor give a reference to a conceptual or theoretical framework.

RW3: More substantively, the rationale for the study doesn't really make a clear case for including epidemic outbreaks and AMR in the same analytic framework and data collection exercise. These types of health threats can be driven by quite different societal, economic, epidemiological factors, to the extent that grouping may obscure more than it reveals. At minimum I'd suggest that the authors spend some time and text discussing why these types of health threats should be considered together, and ideally, what analytic leverage could be gained (and lost) by going this route.
Response: Thank you for your input. In our opinion it makes sense to review both topics together. AMR can be linked to viral conditions because of secondary bacterial conditions, such as pneumonia or sepsis (see MacIntyre and Bui's 2017)1 and because of antiviral drug resistance, which is the case e.g. for influenza (CDC 2016).2 Furthermore, the inclusion of epidemic outbreaks and AMR in the same analytic framework was predefined by the EU Horizon 2020 Work Programme 2018-2020 (Health, demographic change and wellbeing: SC1-HCO-06-2018; https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/sc1-hco-06-2018).

RW3: On p. 6, more explanation for why the PICO tool is being introduced would be helpful. What purpose does this particular framework serve? Is it to guide identification of tools (ie. a search method) or their assessment (a quality assessment framework)?
Response: The PICO framework was used to develop the search strategy (please see line 181, 182).

RW3: p.7: Population
The list of pathogens with pandemic potential seems problematic. Most of these have zero pandemic potential: lassa, CCHF and RVF can cause localized epidemics, but not global spread. (relatedly: the authors could and should include a definition for infectious disease threat — this is the first time that pandemic risk is introduced as the key threshold of interest. Perhaps epidemic risk would make more sense)? The exclusion of coronaviruses (SARS, MERS), is also a strange omission.
Response: Thank you, we overall agree with your comment and deleted the word "pandemic". We revised the paragraph accordingly (line 189-199). SARS and MERS were implicitly included in the search strategy as we used search terms such as "infectious diseases" or "zoonotic diseases".

RW3: pp. 8-9: information sources
the authors should be commended for seeking information from the grey literature, especially assessments by operational NGOs. It may also be fruitful to seek guidance from humanitarian communities of practice (SPHERE-related, ALNAP, WHO emergencies unit), to identify operational assessment tools. Other NGOs could include IRC, CARE. The World Bank may also have relevant tools, and certainly has vulnerability assessment methodologies.
Response: Thank you, we agree that the mentioned organizations could provide valuable input. We will additionally contact them.

RW3: p. 10: inclusion criteria
the focus on particular geographies (Uganda, Ukraine, Bangladesh) is introduced here for the first time. The meaning and implications of this choice are not quite clear, since the study also remains

global (e.g. are the authors doing an exhaustive search but expending extra effort to capture tools from these countries? if so, why? are these context particularly interesting or representative of some broader set of country or contextual types? All of this should ideally be outlined in the protocol.
Response: We have a special interest in tools applied in Bangladesh, Uganda und Ukraine because they are SoNAR-Global partner countries and will pilot one of these tools (line 339-345). However, for greater clarity we added this explanation in the manuscript (please see line 74, 75).

RW3: p. 11
Here the protocol briefly discusses the outcome of the analysis: an analysis and comparison of the vulnerability assessment tools, and their strengths, weaknesses and gaps. It's unclear how the tools will actually be assessed: according to which criteria, and how these criteria will be measured. This is of course critical. Ideally the protocol would include the framework that the coders will use, as well as a rationale for the variables of interest. How should a vulnerability assessment tool be assessed? According to its design, how it requires that users gather and integrate data? It's not clear from the text in this draft, but an argument as to what matters would be important both to the success of the study, and to the literature more broadly.
Response: Thank you for your comment. We rewrote the section on outcomes and variables (line 215-226 and line 319-328).

Reviewer 4 (Mabel Carabali, McGill University, Canada)
RW4: The manuscript is a document considering an important public health topic. The document includes a protocol for a scoping review about vulnerability assessment tools for infectious diseases and antimicrobial resistance.
Although the topic is very interesting, and it is an issue of international concern, the document as it is presented would benefit from major modifications before it is considered for publication, as follows: Is the abstract accurate, balanced and complete?
Not necessarily. It includes a lot of information but it could be more concise and present details about the research question and objectives of the review.
Introduction:
The majority of statements require the support of references. Example, the sentence from line 23-27 in page 4, as the following two sentences in the same paragraph and the rationale statement.
The entire section could be more concise, provide more definitions and present a clear research question. For example, "vulnerability" is not defined anywhere in the text, therefore the context for the review has not been clearly described. A brief mention of "vulnerable populations" was made in line 57 of page 4 but a definition of this or any other of the variables mentioned to be explored in the scoping review is not provided.
Response: Many thanks for your valuable input. We rewrote the abstract, introduction and objectives accordingly (please see line 32-48 and 89-172). Furthermore, we added a section on vulnerability in the introduction (please see line 124-141). We also included the requested references (please see line 91-104).

RW4: Methods:
Is the study design appropriate to answer the research question? Yes, however, further clarifications need to be made. For instance, There is no indication (in the methods or in the rationale) about the selection of the conditions to be studied. Furthermore, there is a broad scope in terms of EIDs but the mentioned ones are viral conditions, while one of the main topics are AMR, which are related mostly to conditions caused by bacteria.
When presenting the "intervention section", it was mentioned that the authors look for "disease outbreaks or epidemics complicated by AMR, to assess, evaluate, and identify vulnerable groups and practices." It would be important for the eventual reader to understand what it means "complicated by AMR" or how, for instance, Ebola Virus is "complicated by AMR".
Response: Thank you for your feedback. Antimicrobial resistance relates to bacterial, fungal, viral and

parasitic diseases and to antimicrobial drugs such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics (WHO, https://www.who.int/en/news-room/fact-sheets/detail/antimicrobial-resistance).
Influenza virus could be “complicated by AMR” because antibiotic resistance may worsen the impact due to bacterial co-infections like pneumonia or sepsis (MacIntyre and Bui’s 2017). Please consider that we wrote “disease outbreaks or epidemics complicated by AMR”. To prevent misunderstandings, we deleted this part.

RW4: Several outcomes are mentioned in the document, but none is completely described or characterized. How would these outcomes would be ascertained? What specific information would the authors look for in the scoping review? Why would the authors look for data from 1978? Why the authors have a specific focus on Uganda, Ukraine and Bangladesh? Is this due to the availability or support from SoNAR partnership or would the review impact in other ways these countries?
Response: Thank you for this important remark. We now added a description of outcomes in the protocol (please see line 215-226). Why we look for data from 1978 was mentioned in the foodnote: “In 1978, the key role of primary health care in promoting health for everyone was agreed upon in the declaration of Alma Ata. This marks a critical waypoint in considering health and wellbeing also as structurally determined by an individual's relative social positionality - an idea inherent in the concept of vulnerability more generally”. For greater clarity, we moved this part into the main body of the document (line 233-237).
We have a special interest in tools applied in Bangladesh, Uganda und Ukraine because they are SoNAR-Global partner countries and will pilot one of these tools (line 339-345). However, for greater clarity we added this explanation in the manuscript (please see line 74, 75).

RW4: It would be important to describe the “simplified” version of the search strategy for Epistemonikos, Global index Medicus (WHO) and AJOL databases.
Response: Thank you for your comment. Search terms for Epistemonikos, Global index Medicus (WHO) and AJOL databases can now be found in the supplementary file (line 270-271).

RW4: It would be necessary to provide information and/or the rationale about why “certain” epidemiological studies and clinical will not be included and how this impact the review.
Response: Thank you for your comment. We agree that this statement could be misleading. We rewrote the exclusion criteria (please see line 300, 302).

RW4: It would necessary to provide the reference for the Rayyan QCRI application for data screening.
Response: Thank you. The citation is now provided in the text (line 306).

RW4: Although it is understandable that a definitive data extraction chart does not exist at this stage; the manuscript would be improved, and its content would contribute more to the scientific community, if a template of the extraction sheet is provided.
Response: Thank you for this valuable input. Please note that all of the authors have a social science background and the way we extract the data most likely resembles a thematic analysis. Therefore, variables will be defined inductively (variables come up while familiarizing with the data) and deductively. For better clarity we rewrote this part (line 319-328).

RW4: Based on the PRISMA-P checklist, several other items are missing in the proposed protocol. For example:
• The rationale has not been comprehensively presented.
• The list and definitions of the variables has not been comprehensively presented/addressed.
• The list and definitions of the outcomes has not been comprehensively presented/addressed
• Risk of bias was not assessed. This is important because despite the qualitative nature of the review, there should be a measure to address bias in the reviewed literature.

• Information about how the data would be synthetized is not present.
• Information about the assessment of the quality of the data was not presented.
Response: Thank you. We rewrote the rationale of the study and provided more information on variables and outcomes in the manuscript (line 90-141, line 215-226, line 319-328).
We will map existing studies irrespective of quality or risk of bias. We refer to the Joanna Briggs Institute Reviewers' Manual 2015 "Methodology for JBI Scoping Reviews" which states for example: "(…) unless otherwise specified, a formal assessment of methodological quality of the included studies of a scoping review is generally not performed" (Peters et al. 2015:8). We mentioned this information in the manuscript (line 330, 331).
As for the data synthesis, the results of the scoping review will be presented in a table. A narrative summary of the findings and how they relate to the overall objectives will be provided (line 334, 335).

FORMATTING AMENDMENTS (if any)
Required amendments will be listed here; please include these changes in your revised version:
● Kindly remove Appendix in your Main Document and upload it separately under file designation "Supplementary File" in PDF Format.
Response: We removed the Appendix in the main document and uploaded a supplementary file

● Strengths and limitations of this study' should consist of 3-5 bullet points. Please ensure that you have met the required number of bullets.
Response: We removed one bullet point from "strengths and limitations".

● Patient and Public Involvement:
Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'.
This should provide a brief response to the following questions:
How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences?
How did you involve patients in the design of this study?
Were patients involved in the recruitment to and conduct of the study?
How will the results be disseminated to study participants?
For randomised controlled trials, was the burden of the intervention assessed by patients themselves?
Patient advisers should also be thanked in the contributorship statement/acknowledgements.
If there is no patient involved in the study, please state "No patient involved" under the sub-heading 'Patient and public involvement'.
Response: We added the information that no patients were involved (line 347-348).

References:
1. MacIntyre CR, Bui CM. Pandemics, public health emergencies and antimicrobial resistance - putting the threat in an epidemiologic and risk analysis context. Archives of Public Health 2017:75:54.
2. CDC. Antiviral Drug Resistance among Influenza Viruses 2016. https://www.cdc.gov/flu/professionals/antivirals/antiviral-drug-resistance.htm, (accessed 2019 August 15)

VERSION 2 – REVIEW

REVIEWER	Mabel Carabali MD, MSc, PhD(c) McGill University, Canada
REVIEW RETURNED	12-Sep-2019

GENERAL COMMENTS	The manuscript has been reviewed and overall recommendations/comments have been adequately addressed by the authors.